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## Extended Hamiltonian approach to continuous tempering

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We introduce an enhanced sampling simulation technique based on continuous tempering, i.e., on continuously varying the temperature of the system under investigation. Our approach is mathematically straightforward, being based on an extended Hamiltonian formulation in which an auxiliary degree of freedom, determining the effective temperature, is coupled to the physical system. The physical system and its temperature evolve continuously in time according to the equations of motion derived from the extended Hamiltonian. Due to the Hamiltonian structure, it is easy to show that a particular subset of the configurations of the extended system is distributed according to the canonical ensemble for the physical system at the correct physical temperature.

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Rapid accurate sampling of the configuration space of a molecular system has been a long-standing challenge in computational molecular science. Molecular systems are typically characterized by rough energy landscapes and the existence of long-lived metastable states separated by high free-energy barriers. This means that the time step required for an accurate simulation is often many orders of magnitude smaller than the typical time necessary to observe a transition between two metastable states. To enhance the sampling efficiency of simulations several methods have been developed in recent years [1–11]. Underpinning one class of such methods is the fact that energetic barriers can be overcome at higher temperature. For example, simulated [2] and parallel tempering (also known as replica exchange) [3,4] are based on this observation. In these methods a discrete distribution of temperatures is chosen and the system hops between these according to a Metropolis criterion preserving the correct distribution at every temperature. One of the issues limiting the efficiency of this approach is the fact that, as the system size increases, the overlap between ensembles at different temperatures diminishes, thus the probability of accepting a jump from one temperature to another is reduced as the dimension is scaled up.

In this article we present an enhanced sampling method based on continuous tempering, i.e., on varying the temperature of the system smoothly. Our approach is based on an extended Hamiltonian formulation in which the physical system is coupled to an additional degree of freedom (with corresponding momentum) in such a way that different values of the coupling parameter correspond to different effective temperatures for the physical system. Equations of motion can be derived in the usual manner from the extended Hamiltonian. The physical system and its effective temperature evolve continuously in time, the latter being determined by the value of the auxiliary degree of freedom. The underlying Hamiltonian structure allows us to show easily that a particular subset of the configurations of the extended system is distributed according to the canonical ensemble for the physical system at the correct temperature.

The method is based on a very simple and mathematically straightforward formulation and gives ample space for

optimization as one can, in principle, tune the distribution of temperatures according to one's desire. Moreover, it is quite flexible as it allows us to act not only on the temperature but also on single terms of the potential energy in a way similar to Hamiltonian replica exchange [5].

Consider a general  $d$ -dimensional system with the associated Hamiltonian  $H(q, p) = p^T M^{-1} p / 2 + U(q)$ . We add to the system a single auxiliary degree of freedom  $\xi$ , with associated momenta  $p_\xi$ . The Hamiltonian of this extended system takes the form

$$\hat{H}(q, p, \xi, p_\xi) = H(q, p) - f(\xi)G(q, p) + p_\xi^2 / 2m_\xi + \phi(\xi), \quad (1)$$

where  $G(q, p)$  is an arbitrary function of  $q$  and  $p$ , e.g.,  $G(q, p) = H(q, p)$  or  $G(q, p) = U(q)$ ,  $\phi(\xi)$  is a confining potential, and  $f(\xi)$  is an arbitrary coupling function that may take any convenient form as long as (i)  $f(\xi) < 1$  and (ii)  $f(\xi) = 0$  for  $|\xi| < \Delta$ . A simple choice is a piecewise even polynomial sigmoidal function with support in  $|\xi| > \Delta$  that switches between zero and a given maximal value in a finite interval  $[\Delta, \Delta']$  (see the inset in the right panel of Fig. 1 for a concrete example). The equations of motion associated with Eq. (1) are

$$\frac{dq}{dt} = \partial_p \hat{H} = \partial_p H - f(\xi) \partial_p G, \quad (2)$$

$$\frac{dp}{dt} = -\partial_q \hat{H} = -[\partial_q H - f(\xi) \partial_q G], \quad (3)$$

$$\frac{d\xi}{dt} = \partial_{p_\xi} \hat{H} = m_\xi^{-1} p_\xi, \quad (4)$$

$$\frac{dp_\xi}{dt} = -\partial_\xi \hat{H} = \partial_\xi f(\xi)G - \partial_\xi \phi(\xi). \quad (5)$$

In these equations the evolution of the physical system is governed by the usual terms plus a contribution depending on  $G$  whose magnitude is modulated by the function  $f$ . The canonical probability density distribution associated with the extended system is  $\hat{\rho}(q, p, \xi, p_\xi) \propto e^{-\beta \hat{H}(q, p, \xi, p_\xi)}$ , where  $\beta^{-1} = k_B T$ ,  $T$  being the physical temperature and  $k_B$  Boltzmann's constant. In particular, in the case  $G(q, p) = H(q, p)$ , for any fixed  $\xi^*$  we have

$$\int dp_\xi \hat{\rho}(q, p, \xi^*, p_\xi) \propto e^{-\beta[1-f(\xi^*)]H(q, p)}, \quad (6)$$

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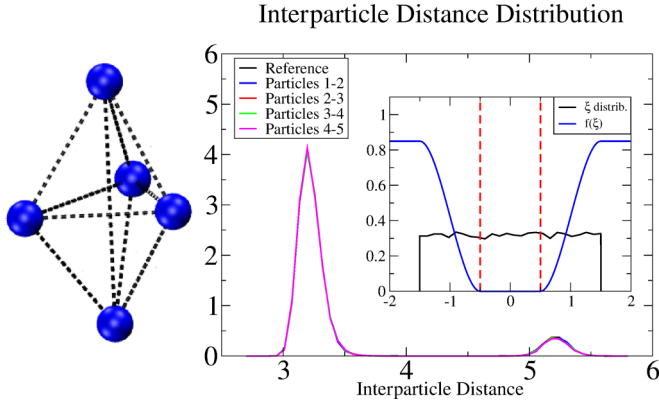


FIG. 1. (Color online) Shown on the left is the system under consideration in its typical double tetrahedron configuration. On the right is the interparticle distance distribution. The reference distribution, computed as described in the text, is compared to the distribution of distances between single pairs obtained using our method. The inset shows, in black, the distribution of the additional degree of freedom  $\xi$ . The function  $f(\xi)$  is shown in blue. The dashed red lines delimit the range of  $\xi$  for which  $f = 0$ . Configurations of the physical system corresponding to these values are canonically distributed at the physical temperature.

which is the canonical distribution of the original system at a modified temperature, i.e., with  $\tilde{T} = T/[1 - f(\xi^*)]$ . Whatever choice of  $G(q, p)$  is made, for  $|\xi^*| < \Delta$  we have  $f = 0$  and  $\int dp_\xi \hat{\rho}$  becomes proportional to the canonical distribution of the original system at the appropriate temperature. It is clear how the dynamics of such an extended system can facilitate overcoming barriers when  $f(\xi) > 0$ . One may just simulate the dynamics of the extended system coupling Eq. (5) with a desired thermostating scheme and ultimately recover the canonical distribution of the original physical one retaining only the physically meaningful configurations for which  $|\xi| < \Delta$ . We remark that this is possible only because of the extended Hamiltonian structure that allows us to relate the stationary distribution of the physical system to that of the extended one. The same procedure would be impossible to apply if, instead of relying on an extended Hamiltonian, one drives the physical system directly into a random walk in temperature over time with some protocol.

Importantly, we can also cast the dynamics of the extended system in a way that the physical system actually experiences a direct change of temperature instead of an equivalent, in terms of sampled stationary distribution, rescaling of the Hamiltonian by a factor  $1 - f(\xi)$ . Choosing  $G(q, p) = H(q, p)$  and postulating the following set of stochastic differential equations (SDEs) to govern the dynamics of the extended system:

$$dq = M^{-1} p dt, \quad (7)$$

$$dp = -\partial_q H dt - \gamma p dt + \sqrt{2\gamma \tilde{\beta}^{-1}(\xi)} M^{1/2} dW, \quad (8)$$

$$d\xi = m_\xi^{-1} p_\xi dt, \quad (9)$$

$$dp_\xi = h(q, p, \xi) dt - \gamma_\xi p_\xi dt + \sqrt{2\beta^{-1} \gamma_\xi m_\xi} dW_\xi, \quad (10)$$

with  $\tilde{\beta}^{-1}(\xi) = k_B T(\xi) \equiv k_B T/[1 - f(\xi)]$ ,  $\gamma$  is a friction coefficient,  $dW$  and  $dW_\xi$  are Wiener processes [12], and  $h(q, p, \xi)$  is an unknown function. These equations imply that the physical system evolves according to a Langevin dynamics in which its temperature depends explicitly on  $\xi$ . The additional degree of freedom and its momentum evolve as well according to a Langevin equation with the temperature constant and equal to the physical one,  $\gamma_\xi$  and  $m_\xi$  being the associated friction and mass, respectively.

We require that Eqs. (7)–(10) have, as stationary distribution,

$$\begin{aligned} \hat{\rho}(q, p, \xi, p_\xi) &:= C \exp \left[ -\tilde{\beta}(\xi) H(q, p) - \beta \left( \phi(\xi) + \frac{p_\xi^2}{2m_\xi} \right) \right] \\ &= C \exp \left[ -\beta [1 - f(\xi)] H(q, p) - \beta \left( \phi(\xi) + \frac{p_\xi^2}{2m_\xi} \right) \right] \\ &= C e^{-\beta \hat{H}(q, p, \xi, p_\xi)}, \end{aligned} \quad (11)$$

where  $C$  is a normalization constant. The SDEs (7)–(10) give rise to an evolution operator for the evolving probability density of the form [12]

$$\begin{aligned} \mathcal{L}^* \rho &= -\partial_q (\partial_p H \rho) + \partial_p [(\partial_q H + \gamma p) \rho] - \partial_\xi (m_\xi^{-1} p_\xi \rho) \\ &\quad + \partial_{p_\xi} \{ [\gamma_\xi p_\xi - h(p, q, \xi)] \rho \} + \partial_p [\gamma m \beta^{-1}(\xi) \partial_p \rho] \\ &\quad + \partial_{p_\xi} (\gamma_\xi m_\xi \beta^{-1} \partial_{p_\xi} \rho). \end{aligned}$$

Demanding stationarity of  $\hat{\rho}$  leads to the requirement

$$h(q, p, \xi) = \partial_\xi f(\xi) H(q, p) - \partial_\xi \phi(\xi), \quad (12)$$

i.e., apart from the viscous drag, the deterministic force acting on  $\xi$  has the same expression of Eq. (5).

For the sampling procedure to be effective the dynamics of the extended system must be such that the additional degree of freedom  $\xi$  effectively diffuses in the interval  $[-\Delta', \Delta']$ . The simplest way to achieve this is to set  $\phi(\xi)$  to be a confining potential, using, for instance, polynomial terms, and bias the dynamics of the extended system along  $\xi$ , in the interval  $[-\Delta', \Delta']$ , using an adaptive biasing technique such as metadynamics [6] or adaptive biasing force [7]. In this way the distribution of  $\xi$  will be flat in such interval. As a consequence, the distribution of temperatures experienced by the physical system is determined only by the form of the function  $f$ , which can be designed to obtain a particular distribution if needed.

First we apply the method to a simple cluster of five particles of mass  $m = 1$  interacting through a pairwise Lennard-Jones potential  $U_{ij} = \epsilon [(\frac{\sigma}{r_{ij}})^{12} - (\frac{\sigma}{r_{ij}})^6]$  with  $r_{ij}$  being the distance between particle  $i$  and particle  $j$  and  $\epsilon = 1$  and  $\sigma = 2.82$  in arbitrary units. At low temperature, the typical configuration of the system is a double tetrahedron (see Fig. 1, left panel) with two particles placed at the vertices and the remaining three forming the common base. The symmetry of the system implies that any possible permutation of the particles position corresponds to a different, but geometrically and energetically equivalent, state. However, at low temperature, dynamical transitions between these states are hindered by the height of the energetic barrier between them.

We aim to calculate the interparticle distance distribution between two given particles. Integrating the Langevin equations of motion for the system setting  $k_B T = 0.05$  and using the Langevin *BAOAB* scheme [13], with a time step  $dt = 0.02$  and a unitary friction  $\gamma = 1$ , for  $1.4 \times 10^7$  time steps does not show a single conformational transition. In this case it is impossible to recover the correct interparticle distance distributions using only two given particles as their distance

simply oscillates weakly around its initial value as the particles never change their position in the double tetrahedron during the simulation. However, due to the symmetry of the system, from this simulation it is possible to compute the correct statistics of the reciprocal distance between two particles considering all the possible ( $5 \times 4/2 = 10$ ) pairs of particles.

We apply our enhanced sampling method choosing  $G(q, p) = H(q, p)$  and we define  $f(\xi)$  in the following way:

$$\begin{aligned} f(\xi) &= 0, \quad |\xi| < \Delta, \\ f(\xi) &= S_f \left[ 3 \left( \frac{|\xi| - \Delta}{\Delta' - \Delta} \right)^2 - 2 \left( \frac{|\xi| - \Delta}{\Delta' - \Delta} \right)^3 \right], \quad \Delta < |\xi| < \Delta', \\ f(\xi) &= S_f, \quad |\xi| > \Delta', \end{aligned} \quad (13)$$

with  $\Delta = 0.5$  and  $\Delta' = 1.5$ . The maximum value of  $f$  is given by  $S_f = 0.85$  (see the inset in right panel of Fig. 1).

We simulate the dynamics of the extended system, in the form given by Eqs. (7)–(10), for  $1.4 \times 10^7$  time steps with  $\gamma_\xi = m_\xi = 1$  and applying the Itô convention [12] for the position-dependent noise in Eq. (8). Accurate integration of the equations of motion in this case is nontrivial. If we seek an integration scheme that mimics the accurate Langevin *BAOAB* scheme [13], we need to introduce an additional splitting of the  $\xi$  evolution with respect to the physical system. This is necessary to correctly treat the position-dependent noise term appearing in Eq. (8) and the  $p$  dependence of  $h(q, p, \xi)$  in Eq. (10) [where the explicit expression of  $h(q, p, \xi)$  is given by Eq. (12)]. In practice, if we consider the convention for additive splitting

$$\begin{aligned} \begin{bmatrix} dq \\ dp \\ d\xi \\ dp_\xi \end{bmatrix} &= \underbrace{\begin{bmatrix} M^{-1}p \\ 0 \\ 0 \\ 0 \end{bmatrix}}_A dt + \underbrace{\begin{bmatrix} 0 \\ -\partial_q H dt \\ 0 \\ 0 \end{bmatrix}}_B dt + \underbrace{\begin{bmatrix} 0 \\ 0 \\ m_\xi^{-1} p_\xi \\ 0 \end{bmatrix}}_{A_\xi} dt + \underbrace{\begin{bmatrix} 0 \\ 0 \\ 0 \\ h(q, p, \xi) \end{bmatrix}}_{B_\xi} dt \\ &+ \underbrace{\begin{bmatrix} 0 \\ -\gamma p dt + \sqrt{2\gamma\beta^{-1}(\xi)} M^{1/2} dW \\ 0 \\ 0 \end{bmatrix}}_O + \underbrace{\begin{bmatrix} 0 \\ 0 \\ 0 \\ -\gamma_\xi p_\xi dt + \sqrt{2\beta^{-1}\gamma_\xi m_\xi} dW_\xi \end{bmatrix}}_{O_\xi}, \end{aligned} \quad (14)$$

the sequence  $BAB_\xi A_\xi O_\xi O O_\xi A_\xi B_\xi AB$  will serve the purpose.

As suggested before, we use a simple confining polynomial potential for  $\phi(\xi)$  and we bias the dynamics of the extended system in  $\xi$  using metadynamics [6,14] in order to have a uniform distribution of  $\xi$  in the interval  $[-\Delta', \Delta']$ . In this way, the system spends about 30% of the time at the physical temperature (the distribution of  $\xi$  obtained from the dynamics, after the metadynamics bias potential has converged, is shown in the inset of the right panel of Fig. 1). The right panel of Fig. 1 shows the obtained distribution density function of the distance between two particles for four different pairs of particles. Each distribution has been calculated using only the statistics of the distance relative to those two particles. The same panel also shows the reference distribution obtained, as described above, from the bare simulation of the physical system gathering the statistics of all the possible different pairs of particles. All of the distributions agree well with the reference and in relation

to one another, demonstrating that the method effectively enhances the sampling of the physical system while preserving the canonical distribution. Corruption of canonical sampling would be immediately identifiable by variations of the width of the density peaks with respect to the reference distribution.

To test the effectiveness of our procedure on more realistic systems we have implemented it in NAMD-lite [15] using the MIST plug-in [16]. For the sake of simplicity of implementation we have made the choice  $G(q, p) = U(q)$ , i.e., the additional degree of freedom has the effect of rescaling only the potential energy and not the whole Hamiltonian or the temperature as in the previous example. Hence, the extended Hamiltonian takes the form

$$\hat{H}(q, p, \xi, p_\xi) = H(q, p) - f(\xi)U(q) + p_\xi^2/2m_\xi + \phi(\xi).$$

The Langevin equations of motion associated with it read

$$dq = M^{-1}p dt, \quad (15)$$



$$dp = -[1 - f(\xi)]\partial_q H dt - \gamma p dt + \sqrt{2\gamma\beta^{-1}} M^{1/2} dW, \quad (16)$$

$$d\xi = m_\xi^{-1} p_\xi dt, \quad (17)$$

$$dp_\xi = [\partial_\xi f(\xi)U(q) - \partial_\xi \phi(\xi)]dt - \gamma_\xi p_\xi dt + \sqrt{2\beta^{-1}\gamma_\xi m_\xi} dW_\xi. \quad (18)$$

Since the rescaling due to the additional degree of freedom acts only on the potential energy there is no strict need to apply the additional splitting of the time evolution operator given in the previous paragraph. Hence, we implement the equation of motions using the simple Langevin *BAOAB* integration scheme [13] treating  $\xi$  as a normal degree of freedom.

For the coupling  $f$  between the physical system and the additional degree of freedom we use the explicit form given by Eq. (13) with  $\Delta = 50$  and  $\Delta' = 150$ . First we apply our method to alanine dipeptide in vacuum. We run the system for 80 ns, saving configurations every 0.1 ps, using a time step of 1 fs and choosing  $\gamma = 1 \text{ ps}^{-1}$ ,  $\gamma_\xi = 10 \text{ ps}^{-1}$ , and  $m_\xi = 10$  in internal NAMD-Lite units. We set  $S_f = 0.8$ ; this value, corresponding to a maximum effective temperature of 1500 K, is certainly too high for an efficient simulation, but we choose this to check eventual corruption of the reconstructed free-energy landscape at the physical temperature. For the confining potential  $\phi(\xi)$  we use a second-order polynomial and we bias the dynamics along  $\xi$  using metadynamics [6,14]. The reconstructed free energy (in units of kcal/mol) as a function of the  $\varphi$  and  $\psi$  dihedral angles is shown in Fig. 2, top panel. This is obtained using only those configurations of the physical system sampled when  $|\xi| < \Delta$ . Looking at these configurations, we can observe 22 independent transition events from the region approximately identified by a value of the angle  $\varphi > 150$  to the region characterized by a value of  $\varphi$  between  $50^\circ$  and  $100^\circ$  (data not shown). For comparison, the bottom panel of Fig. 2 shows the free energy obtained from pure molecular dynamics simulations. This has been obtained by running four independent 1.41- $\mu\text{s}$  simulations (for a total of 5.64  $\mu\text{s}$ ) using the integration routine and the Nosé-Hoover thermostat natively implemented in NAMD-Lite. We used a time step of 1 fs, saving configurations every 20 ps, and we observed in total 28 independent transition events from the region characterized by  $\varphi > 150$  to the one identified approximately by  $50 < \varphi < 100$  (data not shown). It can be observed that the two free-energy profiles are substantially identical.

Next we apply our methodology to a more interesting case, Ala<sub>10</sub> in vacuum. This system has already been used as a nontrivial test case in different studies [17,18]. We aim to calculate the free energy of the system as a function of the end-to-end distance of the molecule (more precisely as a function of the distance between the two extremal carbonyl groups' carbon atoms as done in [18]). The system has a long-lived metastable state consisting of a helical conformation characterized by an end-to-end distance of about 14 Å and several very low probability states with an end-to-end distance between 4 and 12 Å.

We use the same setup used for alanine dipeptide but in this case we set  $S_f = 0.55$ , equivalent to a maximum effective temperature of about 667 K. For the simulation of deca-alanine we also redefined the zero value of the potential energy by

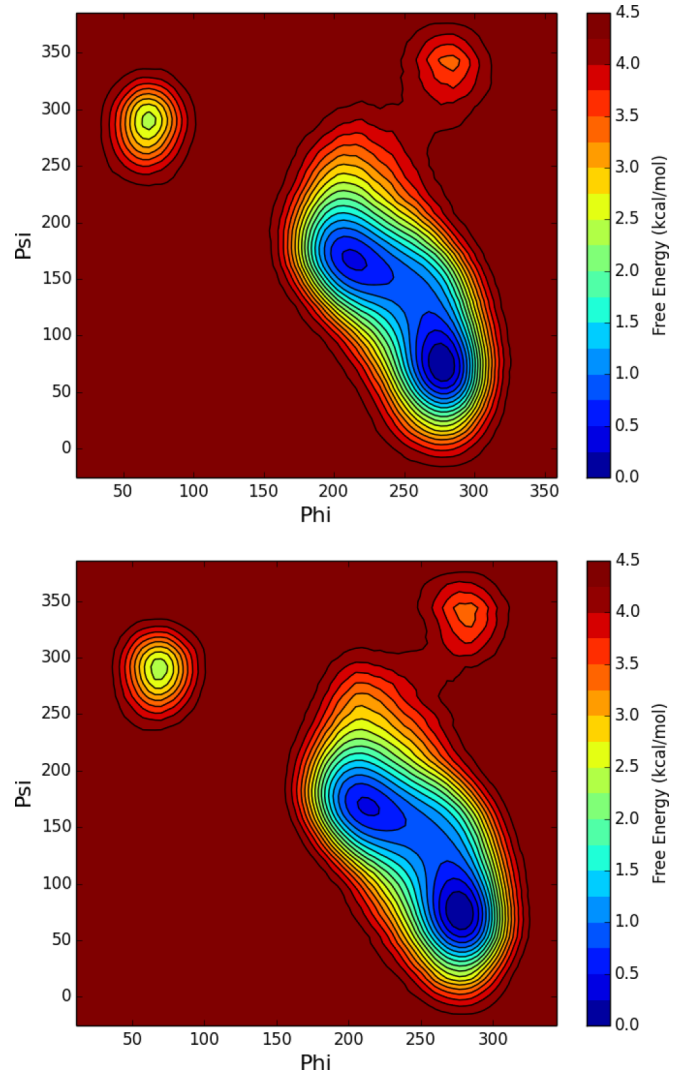


FIG. 2. (Color online) Shown on top is the free energy of alanine dipeptide as a function of the  $\varphi$  and  $\psi$  dihedral angles obtained with our tempering scheme. The bottom is the same quantity obtained from four independent molecular dynamics simulations, in total 5.64  $\mu\text{s}$  long, using the integrator and the Nosé-Hoover thermostat natively implemented in NAMD-Lite. Both plots were obtained by dividing the  $(\phi, \psi)$  space into  $70 \times 70$  bins and then applying a smoothing with a width of three bins.

subtracting its average value (200 kcal/mol) computed from a short simulation of a few picoseconds. This does not have any influence on the results obtained and the reason for doing it is that in Eq. (18) the value of the potential energy of the physical system determines the value of the force acting on the auxiliary degree of freedom. Hence, it is easily seen how adding to the potential energy a constant that makes its average value closer to zero facilitates the diffusion of  $\xi$  from the very beginning of the simulation (note, however, that even if this is not done the metadynamics bias will eventually compensate for this effect anyway).

We have simulated the extended system for 900 ns using a time step of 1 fs and the CHARMM22 force field [19], saving configurations every 1 ps. A bare molecular dynamics simulation of this length of the physical system at 300 K will

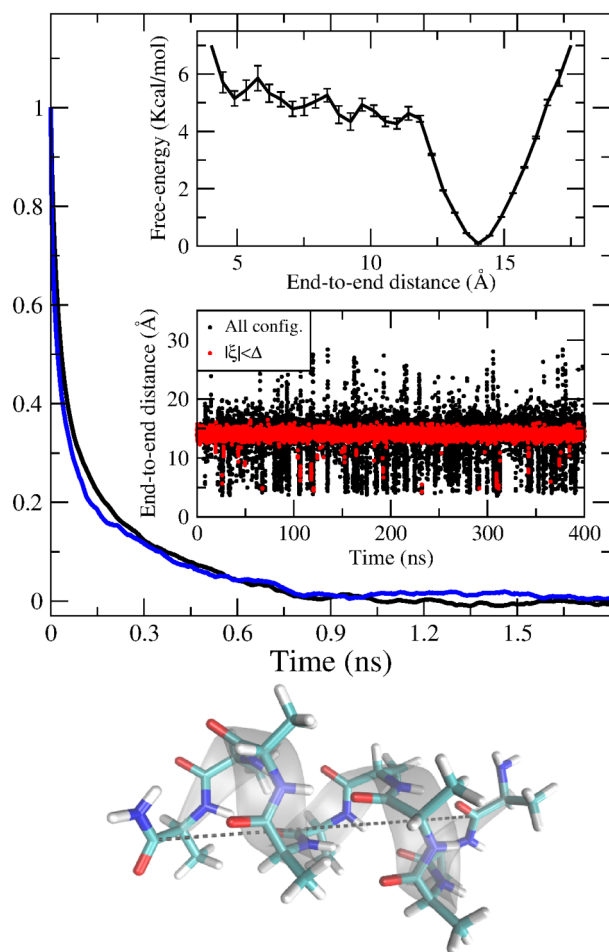
$\xi$  and End-to-end Dist. Autocorrelation Func.

FIG. 3. (Color online) Shown on top is the autocorrelation function of  $\xi$  and of the end-to-end distance (black and blue lines, respectively). The estimated autocorrelation time is less than 100 ps in both cases. The upper inset shows, in black, the evolution of the end-to-end distance during the first 400 ns of simulation and in red the same quantity for the subset of configurations subject to the condition  $|\xi| < \Delta$ . Only the latter were used to compute the free-energy profile shown in the top inset. The bottom shows the deca-alanine molecule in its folded helical state. A dashed gray line connects the two extremal carbonyl carbon atoms used to compute the end-to-end distance.

hardly show any transition. The lower inset in the top panel of Fig. 3 shows, in black, the evolution of the end-to-end distance during the first 400 ns of simulation of the extended system. The molecule frequently visits configurations characterized by a low value of the end-to-end distance and undergoes also a considerable amount of complete unfolding events, characterized by an end-to-end distance greater than 25 Å. The same quantity, but only for the configurations corresponding to values of  $|\xi| < \Delta$ , is shown in red and it can be noticed how almost all configurations are characterized by a value of the end-to-end distance around 14 Å, showing that the procedure is consistent and the high-temperature configurations visited during the simulation do not corrupt the reconstruction of the canonical distribution. From these data we obtained the free-energy profile shown in the upper inset, which is compatible,

within the errors, with the results obtained in Ref. [18]. The top panel of Fig. 3 also shows the autocorrelation function of the additional degree of freedom and of the end-to-end distance (black and blue lines, respectively). The relative autocorrelation times can be estimated in about 80 and 50 ps, respectively.

We have introduced a tempering simulation technique based on an extended Hamiltonian formulation. In our approach, an additional degree of freedom is coupled to the physical system and its dynamical evolution results in a change of the effective temperature of the physical system. In contrast to traditional tempering simulation techniques such as simulated and parallel tempering, in our case the temperature change experienced by the physical system is continuous. In both simulated and parallel tempering, swaps between different discretely distributed temperatures are attempted according to a protocol that preserves detailed balance. A continuous change of temperature may be a convenient advantage since in many cases the discrete distribution of temperatures implies a small overlap between the different ensembles causing the acceptance rate for the attempted swaps to be low.

Other algorithms based on varying the temperature, or similarly on changing the energy distribution of a system using a bias potential, have been proposed in past works, Refs. [20–22] being among the most well known. Our method has certain conceptual similarities to all these techniques. In particular, metadynamics in the well-tempered ensemble [23] consists of applying a bias on the potential energy such that its fluctuations are consistently augmented but maintaining the average value approximately equal to the canonical one. For the interested reader a general discussion, from a foundational perspective, of the similarities between the multicanonical ensemble approach of Refs. [21,22] and metadynamics using the potential energy as a collective variable can be found in [24]. Unlike with these methods, our approach is based on an auxiliary variable whose dynamical evolution has the effect of driving the physical system through different regimes. We use a metadynamics history-dependent potential to flatten the distribution of the auxiliary variable in an interval of interest. The use of Gaussian kernels to obtain a desired target distribution is also at the basis of Ref. [23] and represents a numerically robust framework with respect to the formulation of Refs. [21,22] (see [24] and references therein for details). A continuous tempering technique has also been proposed by Zhang and Ma [25,26]. The main difference between their approach and ours lies in the simplicity and robustness of our formulation. The extended Hamiltonian formulation strongly simplifies the treatment of the dynamical evolution of the temperature. Compared to all these techniques, obtaining a desired temperature (or energy) distribution is very simple in our case since this can be achieved by shaping appropriately the coupling function  $f(\xi)$ . The flexibility of our approach allows us to couple the additional degree of freedom not only to the temperature but also to particular terms of the potential energy known to be relevant. A simple and direct possible example may be a rescaling of the dihedral angles' potential energy term in a way reminiscent of what is done in accelerated MD [9]. With our approach, no reweighing of the sampled configurations is needed since the particular form of the coupling between the physical system and the additional degree of freedom ensures that a certain portion of the

simulation (about 1/3 in the examples presented above) produces samples distributed canonically at the physical temperature, thus consistently alleviating the usual issue characterizing reweighed simulations at high temperature (or rescaled energy)

that affects some of the techniques mentioned, i.e., having very few configurations with high weight dominating the statistics.

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